

REMARKS

Claims 1-17 and 19-27 are pending and presently under consideration, prior to Amendment. Claims 5-17 have been withdrawn from consideration as directed to a non-elected species. Applicants have amended claim 27 to more particularly point out that the method is an *in vitro* method of screening and that the normal lung cells are *provided in culture*. Support for Applicants' amendments are found throughout the specification and previously pending claims. No new matter has been entered.

Applicants cancel, without prejudice, claims 2 and 19-24. Applicants expressly reserve the right to prosecute claims of similar or differing scope in this or future applications.

Applicants add new claim 28. Support for the subject matter of the newly added claim is found throughout the specification and previously pending claims. No new matter has been entered.

Applicants request entry of Applicants' after-final amendments. Applicants' amendments either place the application in condition for allowance or simplify issues for Appeal.

Applicants request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Interview Summary

Applicants thank the Examiner for courtesies extended during a telephonic interview summarized in the Interview Summary mailed by the Examiner on November 26, 2007. As indicated in the Interview Summary, the undersigned contacted the Examiner for clarification regarding whether the instant Office Action was made final.

Status of Application, Amendments, and/or Claims

Applicants note that the amendment of August 27, 2007 has been entered in full. Applicants take this opportunity to correct a typographical error in which claim 27 was omitted from the listing of claims under consideration (See, the third paragraph on page 2 of the Office Action). Applicants note that claim 27 was obviously considered by the Examiner and is specifically addressed on, for example, page 9 of the Office Action. Accordingly, claims 1-17 and 19-27 are pending and under consideration.

Withdrawn Objections and/or Rejections

Applicants note that the objection to claim 21 has been withdrawn.

Applicants note that the rejection of claims 1-4 and 21-26 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement has been withdrawn.

Applicants note that the rejection of claims 1-4 and 22-26 under 35 U.S.C. § 112, second paragraph, has been withdrawn.

Applicants note that the rejection of claim 21 under 35 U.S.C. § 103(a) as allegedly unpatentable over Marigo in view of Fujita has been withdrawn.

Rejection of Claims 2 and 19-24 Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 2 and 19-24 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse the rejection. Applicants note with appreciation that the Examiner has recognized that a claim to contacting embryonic lung tissue from a *Shh* mutant mouse is enabled.

Applicants maintain the arguments of record and contend that the specification provides ample guidance to enable one of skill in the art to practice the claimed invention. Nevertheless, to expedite prosecution, Applicants cancel, without prejudice, claims 2 and 19-24. Applicants' cancellation of claims 2 and 19-24 is not in acquiescence to the rejection or to any of the arguments advanced in the instant Office Actions. Applicants expressly reserve the right to prosecute claims of similar or differing scope in future applications. Further, Applicants expressly reserve the right to present arguments or evidence addressing any of the points raised by the Examiner during prosecution of these claims.

Applicants' cancellation of claims 2 and 19-24 renders the rejection moot. Reconsideration and withdrawal of this rejection are requested.

Rejection of Claims 19 and 20 Under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 19 and 20 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants traverse this rejection.

Applicants maintain the argument of record and contend that the specification provides ample support to satisfy the written description requirement with respect to claims 19 and 20.

Applicants note that the instant claims are not directed to the agents, per se, but rather are directed to screening methods in which agents are tested. As such, Applicants contend that the Examiner's arguments concerning whether the specification explicitly discloses examples of agents possessing particular structural properties is misplaced.

Nevertheless, to expedite prosecution and as detailed above, Applicants cancel, without prejudice, claims 19 and 20. Applicants' cancellation of claims 19 and 20 is not in acquiescence to the rejection or to any of the arguments advanced in the instant Office Action. Applicants expressly reserve the right to prosecute claims of similar or differing scope in future applications. Further, Applicants expressly reserve the right to present arguments or evidence addressing any of the points raised by the Examiner during prosecution of these claims. Cancellation of claims 19 and 20 renders the rejection moot, and reconsideration and withdrawal of the rejection are requested.

Rejection of Claims 1, 3, 4, 25, and 26 Under 35 U.S.C. § 103(a)

Claims 1, 3, 4, 25, and 26 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Marigo *et al.* (US 6,261,786) and Fujita *et al.* (BBRC 238: 658-665, 1997). Applicants traverse this rejection.

Pursuant to MPEP 2142, "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)." The combined teachings of Marigo *et al.* and Fujita *et al.* fail to satisfy these criteria, and thus fail to undermine the patentability of the claimed invention.

Claim 1 (and dependent claims 3, 4, 25, and 26) is directed to screening assays wherein a combination of two parameters is specifically determined. In other words, the claimed methods provide assays in which agents are screened based on an evaluation of two parameters: (i)

whether the agent inhibits or attenuates hedgehog signaling and (ii) whether the agent inhibits or reduces cell proliferation or growth.

In contrast, Marigo *et al.* fail to teach or suggest assays in which screening is based on evaluating multiple parameters. (See, column 8, lines 66-67 through column 10, lines 1-6). This deficiency of Marigo *et al.* is not overcome by the teachings of Fujita *et al.* Not only is Fujita *et al.* silent as to the use of small molecules, but Fujita *et al.* fail to teach or suggest assays in which screening is based on evaluating multiple parameters. In other words, both Marigo *et al.* and Fujita *et al.* teach methods in which a single parameter is evaluated following contacting cells with an agent. Neither reference teaches the use of multiple parameters, and neither reference suggests the desirability of screening based on evaluating multiple parameters. The fact that Marigo *et al.* and Fujita *et al.* evaluate different parameters does not provide any teaching or suggestion for a screening method based on evaluating multiple parameters. The fact that each reference describes screens based on analysis of one parameter teaches away from methods based on analyzing multiple parameters, as there is no motivation to design a more involved assay (e.g., an assay involving multiple analytic steps). Thus, regardless of whether the analysis of antibodies in Fujita *et al.* provides a reasonable expectation of success in screening for small molecule inhibitors (a point which Applicants do not concede), the combined teachings of Marigo *et al.* and Fujita *et al.* fail to teach or suggest each and every limitation of the claimed invention for, at least, failing to teach or suggest screening assays in which agents are evaluated based on multiple parameters. Further, one of skill in the art would not have been motivated to alter and extend the teachings of Marigo *et al.* and Fujita *et al.* to arrive at the claimed invention. In other words, the design and use of screening methods that employ analysis of multiple parameters in neither taught nor suggested by the prior art. As such, the combined teachings of Marigo *et al.* and Fujita *et al.* fail to satisfy the criteria for rendering the claimed invention obvious.

The standard for obviousness under 35 U.S.C. §103 asks whether the claimed invention, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. An obviousness analysis requires the four factual determinations set forth in *Graham v. John Deere*, 148 USPQ 459 (1966). See also MPEP § 2141; *KSR Int'l Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (2007). The Examiner has the burden of factually supporting any conclusion of obviousness, which includes findings of objective evidence of a teaching, motivation, or

suggestion to select and combine the references relied on as evidence of obviousness. *See* MPEP § 2142. In the present case, Applicants contend that the claimed invention, taken as a whole, provides screening assays based on determining multiple parameters. This invention is not rendered obvious by the teachings of Marigo *et al.* and Fujita *et al.*

Applicants note that the Court in *KSR* did not disrupt the necessity of the factual inquiry set forth in *Graham*. Further, the Court in *KSR* did not jettison the teaching, motivation, or suggestion test. Rather, the Court clarified that, in circumstances of predictable arts, common sense may provide the requisite teaching, suggestion, or motivation. Further, *KSR* did not alter the basic requirements for establishing a *prima facie* case of obviousness (the references must teach or suggestion each and every limitation of the claimed invention; there must be a suggestion to combine the references; and there must be a reasonable expectation of successfully combining the references to arrive at the claimed invention). As such, the Examiner still has the initial burden of establishing a *prima facie* case of obviousness.

Applicants contend that the combined teachings of Marigo *et al.* and Fujita *et al.* fail to undermine the patentability of the claimed invention. The cited references, considered alone or in combination, fail to teach or suggest screening assays based on determining multiple parameters. Further, the presence of multiple examples in the literature in which agents are assessed based on evaluation of a single parameter provides no suggestion or motivation to design assays based on determining multiple parameters. Accordingly, reconsideration and withdrawal of this rejection are requested.

Rejection of Claim 27 Under 35 U.S.C. § 103(a)

Claim 27 is rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Marigo *et al.* in view of Bellusci. Applicants traverse this rejection.

Applicants arguments above with respect to the rejection of claims 1, 3, 4, 25, and 26 under 35 U.S.C. § 103(a) as allegedly unpatentable over Marigo *et al.* (US 6,261,786) and Fujita *et al.* (BBRC 238: 658-665, 1997) are equally applicable to the instant rejection. As detailed above, the claimed methods provide assays wherein a combination of two parameters is specifically determined. In other words, the claimed methods provide assays in which agents are screened based on an evaluation of two parameters: (i) whether the agent inhibits or attenuates hedgehog signaling and (ii) whether the agent inhibits or reduces cell proliferation or growth.

The cited references fail to teach or suggest each and every element of the claimed invention, and thus fail to satisfy the criteria necessary for rendering the claimed invention obvious.

Further, reliance on Bellusci is based on the Examiner's interpretation of the term "normal" as describing the location of the tissue (i.e., tissue found in its normal location). Applicants submit that this interpretation is not the most reasonable interpretation of the term "normal" when read in the context of the present application and claims. Rather, the term normal is used to contrast the lung cells for use in the claimed method from cancerous or otherwise diseased cells.

Nevertheless, to expedite prosecution, Applicants have amended claim 27 to more particularly point out that the claimed method is an in vitro method and that the normal (i.e., non-diseased) cells are provided in culture. Applicants' amendment is not in acquiescence to the rejection. Applicants reserve the right to prosecute claims of similar or differing scope in this or future applications. Applicants reserve the right to present additional or alternative arguments to address any or all of the points raised by the Examiner herein.

Applicants contend that, prior to Amendment, the combined teachings of Marigo *et al.* and Bellusci fail to satisfy the criteria necessary to render the claimed invention obvious. For example, the combined teachings of Marigo *et al.* and Bellusci fail to teach or suggest each and every limitation of the claimed invention. The deficiencies of the combined teachings of the cited references are further underscored by Applicants' amendment.

As detailed above, neither Marigo *et al.* nor Bellusci teach or suggest assays in which screening is based on evaluating multiple parameters. In other words, both Marigo *et al.* and Bellusci teach methods in which a single parameter is evaluated. Neither reference teaches the use of multiple parameters, and neither reference suggests the desirability of screening based on evaluating multiple parameters. The fact that Marigo *et al.* and Bellusci evaluate different parameters does not provide any teaching or suggestion for a screening method based on evaluating multiple parameters. The fact that each reference describes screens based on analysis of one parameter teaches away from methods based on analyzing multiple parameters, as there is no motivation to design a more involved (e.g., an assay involving multiple analytic steps). Thus, the combined teachings of Marigo *et al.* and Bellusci fail to teach or suggest each and every limitation of the claimed invention for, at least, failing to teach or suggest screening assays in which agents are evaluated based on multiple parameters. Further, one of skill in the art would

not have been motivated to alter and extend the teachings of Marigo *et al.* and Bellusci to arrive at the claimed invention. As such, the combined teachings of Marigo *et al.* and Bellusci fail to satisfy the criteria for rendering the claimed invention obvious.

The standard for obviousness under 35 U.S.C. §103 asks whether the claimed invention, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. An obviousness analysis requires the four factual determinations set forth in *Graham v. John Deere*, 148 USPQ 459 (1966). *See also* MPEP § 2141; *KSR Int'l Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (2007). The Examiner has the burden of factually supporting any conclusion of obviousness, which includes findings of objective evidence of a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness. *See* MPEP § 2142. In the present case, Applicants contend that the claimed invention, taken as a whole, provides screening assays based on determining multiple parameters. This invention is not rendered obvious by the teachings of Marigo *et al.* and Bellusci.

Applicants note that the Court in *KSR* did not disrupt the necessity of the factual inquiry set forth in *Graham*. Further, the Court in *KSR* did not jettison the teaching, motivation, or suggestion test. Rather, the Court clarified that, in circumstances of predictable arts, common sense may provide the requisite teaching, suggestion, or motivation. Further, *KSR* did not alter the basic requirements for establishing a *prima facie* case of obviousness (the references must teach or suggestion each and every limitation of the claimed invention; there must be a suggestion to combine the references; and there must be a reasonable expectation of successfully combining the references to arrive at the claimed invention). As such, the Examiner still has the initial burden of establishing a *prima facie* case of obviousness.

Applicants contend that the combined teachings of Marigo *et al.* and Bellusci fail to undermine the patentability of the claimed invention. The cited references, considered alone or in combination, fail to teach or suggest screening assays based on determining multiple parameters. Further, the presence of multiple examples in the literature in which agents are assessed based on evaluation of a single parameter provides no suggestion or motivation to design assays based on determining multiple parameters. Accordingly, reconsideration and withdrawal of this rejection are requested.

Rejection of claim 27 Under 35 U.S.C. § 112, first paragraph, (New Matter)

Claim 27 is rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. This is a new matter rejection. Applicants traverse this rejection.

Applicants contend that claim 27 is amply supported by the specification. The specification supports methods for identifying agents that function to reduce or inhibit proliferation or growth of lung cells. Further, the specification clearly contemplated that the subject screening methods could be conducted using any of a range of cells, including diseased cells (cancerous and other diseased cells), as well as non-diseased (e.g., "healthy" cells). Exemplary support can be found, for example, on page 15, lines 12-14; page 15, lines 26-29; page 16, lines 1-4; and page 48, lines 10-20. Thus, contrary to the Examiner's statement, the specification provides broad support for screening methods conducted generally in lung cells, including diseased and non-diseased cells.

Compliance with the written description requirement does not require that the claims find *in haec verba* support in the specification. MPEP 2163.02. When interpreted in the context of the present application, the term "normal" refers to cells, not to their location in vivo, and is clearly used to distinguish the cells for use in the claimed method from cancerous or other diseased cells. Thus, claim 27 complies with the written description requirement regardless of whether the term "normal" is explicitly recited in the specification.

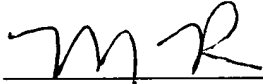
Applicants submit that the specification, taken as a whole, as well as the exemplary passages referenced above, provide sufficient support for claim 27 to satisfy the written description requirement. Accordingly, reconsideration and withdrawal of this rejection is requested.

CONCLUSION

If any clarification of the above response would facilitate prosecution of this application, Applicants respectfully request that the Examiner contact the undersigned at 617-951-7000. Any fee required for timely consideration of this submission may be charged to **Deposit Account No. 18-1945, under Order No. HUIP-P02-032.**

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Respectfully Submitted,



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